Family Cancer History and Susceptibility to Oral Carcinoma in Puerto Rico

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BACKGROUND. Use of alcohol and tobacco are the major risk factors for cancers of the oral cavity and pharynx in most of the world. A heritable component to oral carcinoma risk also has been suggested, although only limited data are available on familial aggregation of this disease.

METHODS. A population-based case–control study of 342 subjects with carcinomas of the oral cavity and pharynx (oral carcinoma) and 521 controls was conducted in Puerto Rico. The relation between family history of carcinomas of the oral cavity, the upper aerodigestive tract (UADT), and other selected sites with risk of oral carcinoma was explored using logistic regression modeling techniques.

RESULTS. Risk of oral carcinoma was elevated for subjects reporting a first-degree relative with carcinoma of the oral cavity (odds ratio [OR], 2.5; 95% confidence interval [CI], 0.8–8.0) or any UADT carcinoma (OR, 2.6; 95% CI, 1.4–4.8). The increased risk associated with family history of UADT carcinoma tended to be greatest for subjects with known risk factors (i.e., heavy consumption of alcohol and/or tobacco and infrequent intake of raw fruits and vegetables) and with oral carcinoma diagnoses at ages younger than 65 years.

CONCLUSIONS. These findings are consistent with a heritable component to oral carcinoma, although shared lifestyle risk factors may be partially involved. ***Cancer* 2001;92:2102–8.** © *2001 American Cancer Society.*

KEYWORDS: alcohol, case–control studies, diet, family, head and neck neoplasms, Puerto Rico, tobacco.

The incidence of oral cavity and pharyngeal carcinomas (excluding lip and nasopharynx) is higher in Puerto Rican men (17.5/100,000) and women (4.5/100,000)[1] than among Hispanic populations in the United States (men, 8.9/100,000; women, 2.7/100,000).[2] To evaluate reasons for these high rates, we conducted a population-based case–control study among male and female residents of Puerto Rico. As previously reported, use of alcohol and tobacco is estimated to account for approximately 76% of oral cavity and pharyngeal carcinomas (hereafter referred to as oral carcinoma) among men and 52% among women in Puerto Rico.[3]

An inherited component of susceptibility to oral carcinoma has been suggested by case reports of families with multiple affected members,[4–6] by epidemiologic studies indicating familial tendency to oral carcinoma or other cancers of the head and neck,[7–15] by segregation analysis in first-degree relatives,[16] by elevated risks associated with polymorphic genes suspected to be involved in the metabolism of tobacco and alcohol,[17–20] and by genes involved in DNA repair and maintenance of genetic stability.[21,22]

This article evaluates the relation between family history of cancer and risk of oral carcinoma among residents of Puerto Rico, in-

cluding possible modification of risks associated with alcohol, tobacco, and diet.

METHODS

Cases and Controls

Methods for selection of cases and controls have been published in detail elsewhere.[23] In brief, eligible cases were all Puerto Rican residents aged 21–79 years with a newly diagnosed histologically confirmed carcinoma of the oral cavity (excluding lip) or pharynx (excluding nasopharynx; International Classification of Diseases for Oncology codes C01–C14)[24] who were diagnosed between December 1992 and February 1995. Of the 519 oral carcinoma cases ascertained, interviews were conducted with 367 (71%). Nonresponse was because of death of patient or patient too ill to participate (18%), patient refusal to be interviewed (5%), or if we were unable to locate (6%).

Population controls were selected from two sources and frequency matched to the cases by age and gender. A two-stage area probability sampling frame of dwelling units in Puerto Rico was used to select controls aged 21–64 years. Computerized listings of Puerto Rican Medicare recipients provided by the Health Care Financing Administration stratified by age and gender were used to select systematically, after a random start, controls aged 65–79 years. Interviews were completed for 521 (83%) of the 629 eligible controls (after excluding 2 potential controls with self-reported histories of oral carcinoma). Reasons for nonresponse were refusal to be interviewed (8%), followed by inability to locate (7%), and deceased or too ill (2%).

Excluded from this analysis were 25 cases with salivary gland carcinoma or an oral tumor with a histologic type suggesting a salivary gland origin.[3] Thus, the final study group for this analysis consisted of 342 cases (286 male, 56 female) and 521 controls (417 male, 104 female).

All subjects gave written informed consent to participate in the study. The study protocol was approved by Institutional Review Boards at the National Cancer Institute and the University of Puerto Rico.

Data Collection

In-person interviews were conducted in Spanish with the cases and controls by trained interviewers, usually in the subject's home. Detailed information was obtained on several factors possibly related to oral carcinoma, including family history of cancer, use of alcohol and tobacco, usual adult diet, usual occupation, medical and dental history, and sociodemographic factors.

The objective of the familial history component of this study was to determine whether oral carcinoma patients were more likely than controls to have a parent or sibling with a reported history of oral cavity carcinoma or any upper aerodigestive tract (UADT) carcinoma (defined as including the oral cavity, pharynx, larynx, esophagus, and "throat"). We also examined risk associated with a family history of non-UADT carcinoma, any type of cancer, and several specific types of cancer (lung, liver, stomach, and male and female reproductive sites). Lung and liver cancers were selected as the most important non-UADT smoking- and drinking-related cancers, respectively, whereas cancers of the stomach and reproductive system were selected because they were the most commonly reported tumors among the relatives of study subjects and thus provided sufficient numbers for analysis.

To ascertain family history of cancer, subjects were told, "Now I would like to ask you about whether any of your blood relatives ever were diagnosed as having cancer" and then asked the following questions. "Did you have any full brothers or sisters?" "How many full brothers or sisters did you have?" "Was your relation (i.e., mother, father, sister, brother) ever diagnosed as having cancer?" If yes, they were asked "What type of cancer did (he/she) have?" and "How old was (he/she) when the cancer was diagnosed?" Subjects were also asked a similar series of questions to ascertain history of cancer in a spouse or significant other.

Data Analysis

Unconditional logistic regression models using the BMDPLR procedure were used to obtain maximum likelihood estimates of adjusted odds ratios (ORs) and approximate 95% confidence intervals (CIs) for the family history of cancer variables of interest.[25,26] Odds ratios were adjusted for the selection factors: age (younger than 54, 55–59 … 65–69, 70 and older) and gender (male, female), and where indicated, the potential confounding variables lifetime tobacco use (no tobacco use, $\leq$ 5,000, 5001–10,000, 10,001–20,000, $>$ 20,000 cigarette packs, and no cigarettes but use of other tobacco) and lifetime drinks of alcohol (no alcohol, $\leq$ 10,000, 10,001–40,000, 40,001–80,000, $>$ 80,000). Several additional potential confounders were evaluated, including education, income, and intake of raw fruits and vegetables, but were not included in the final logistic model because they did not confound the relation between family history of cancer and the risk of oral carcinoma. Odds ratios were assessed for occurrence of cancers in parents, siblings, male relatives (father and/or brother), and female relatives (mother and/or sister). Removal of subjects without a sibling (21 cases, 38 controls) from the sibling variables did

TABLE 1
Risk of Oral and Pharyngeal Carcinoma According to Family History of Upper Aerodigestive Tract Carcinoma[a]

Family history	Cases	Controls	OR[b,c]	95% CI
Any first-degree relative				
Any UADT carcinoma	59	28	2.6	1.4–4.8
Oral cavity carcinoma	13	6	2.5	0.8–8.0
Non-UADT carcinoma	96	166	0.8	0.5–1.2
Either parent				
Any UADT carcinoma	33	22	2.0	1.0–4.2
Oral cavity carcinoma	4	5	0.7	0.1–3.4
Non-UADT carcinoma	122	172	0.9	0.6–1.4
Any sibling				
Any UADT carcinoma	31	9	2.7	1.1–6.7
Oral cavity carcinoma	9	1	12.8	1.4–118.0
Non-UADT carcinoma	124	185	0.9	0.7–1.4
Any male first-degree relative				
Any UADT carcinoma	45	22	2.1	1.1–4.1
Oral cavity carcinoma	7	3	2.6	0.6–11.8
Non-UADT carcinoma	110	172	0.9	0.6–1.3
Any female first-degree relative				
Any UADT carcinoma	18	9	3.3	1.2–9.4
Oral cavity carcinoma	6	3	2.5	0.5–13.8
Non-UADT carcinoma	137	185	1.0	0.7–1.4

OR: odds ratio; CI: confidence interval; UADT: upper aerodigestive tract.
[a] Upper aerodigestive tract carcinomas include oral cavity, pharynx, larynx, esophagus, and "throat."
[b] All ORs relative to risk of 1.0 for 187 cases and 327 controls with no family history of cancer.
[c] All ORs adjusted for age, gender, tobacco, and alcohol.

not alter the risk estimates; thus, they were left in the referent category (no family history of cancer) for consistency of presentation. In general, risks were similar for males and females. Risks for both genders combined are presented in the tables, as the low numbers of female subjects yielded unstable risk estimates for some variables. To determine whether the combined effects of family history of UADT carcinoma with 1) drinking and smoking and 2) intake of raw fruits and vegetables were consistent with multiplicative models, we compared the log likelihoods of logistic models with and without interaction terms. The combined categories of drinking and smoking used in this analysis were formulated based on the risks reported in a detailed analysis of smoking and drinking patterns for this study population presented in Hayes et al.[3]

RESULTS

As shown in Table 1, family history of UADT carcinoma in a first-degree relative was reported by 59 cases (17.2%) and 28 controls (5.4%), yielding an adjusted OR of 2.6 (95% CI ≠ 1.4–4.8). The OR was similar (2.5, 95% CI, 0.8–8.0) for the 13 cases and 6 controls who reported a family history of oral cavity carcinoma. In contrast, there was no excess risk associated with familial occurrence of non-UADT carcinoma (OR, 0.8; 95% CI, 0.5–1.2). Risks were similar for subjects with a UADT carcinoma in siblings, parents, male relatives, and female relatives. The risks of oral carcinoma associated with a family history of UADT carcinoma were similar for males (OR, 2.7; 95% CI, 1.3–5.3; based on 47 cases and 22 controls) and females (OR, 2.4; 95% CI, 0.6–9.5; based on 12 cases and 6 controls). Furthermore, risks were nonsignificantly higher for those younger than 65 years (OR, 4.0; 95% CI, 1.7–9.3, 30 cases and 13 controls) than those age 65 years and older (OR, 2.4; 95% CI, 1.0–5.6; 29 cases and 15 controls). A history of UADT carcinoma was reported for the spouses of 2 cases and 3 controls (OR, 0.3; 95% CI, 0.03–3.1).

Eight cases (five males, three females) and four controls (two males, two females) reported having more than one first-degree relative with a history of UADT carcinoma (Table 2). In these subgroups, the controls all reported at least one affected parent, whereas three of the cases reported multiple affected siblings but no affected parents. In addition, one of the cases and one of the controls reported three affected family members.

Table 3 presents oral carcinoma risks associated with a family history of any cancer and five non-UADT adult carcinomas: one smoking-related carcinoma (lung), one alcohol-related carcinoma (liver), and three types of cancer common in this study population (stomach and male and female reproductive sites). The risk associated with any family history of cancer was 1.1 (95% CI, 0.7–1.5). In addition, no significant elevations or reductions in risk were associated with a history of any specific non-UADT carcinoma.

As shown in Table 4, the overall risks associated with the joint effects of a family history of UADT carcinoma, and the study subject's smoking and drinking status were consistent with independent effects on a multiplicative scale ($P = 0.7$). Risks increased with higher smoking/drinking levels (i.e., light/light to light/heavy or heavy/light to heavy/heavy) among both subjects with and without a family history of UADT carcinoma. However, within each smoking/drinking category, risks were higher for subjects with a family history of UADT carcinoma, ranging from less than twofold for light users of alcohol and tobacco to almost fivefold for heavy users of both. The highest risk (OR, 60.4; 95% CI, 21.0–174.0) was observed for heavy smokers and drinkers with a family history of UADT carcinoma. The results were similar when combined risks were calculated separately for family history in parents and siblings (data not shown). The combined effects of family history of UADT carcinoma and intake of raw fruits and vegeta-

TABLE 2
Subjects with More Than One Parent or Sibling with an Upper Aerodigestive Tract Carcinoma[a]

Status	Gender	Age	No. of sisters	No. of brothers	Family member	Type of UADT carcinoma	Family member	Type of UADT carcinoma	Family member	Type of UADT carcinoma
Case	Male	77	4	8	Father	Throat[b]	Sister	Tongue	Sister	Throat[b]
Case	Male	68	4	5	Mother	Throat[b]	Brother	Oral cavity		
Case	Male	59	6	5	Father	Throat[b]	Brother	Oral cavity		
Case	Male	78	1	7	Brother	Throat[b]	Brother	Throat[b]		
Case	Male	80	1	5	Brother	Throat[b]	Brother	Throat[b]		
Case	Female	66	2	5	Mother	Esophagus	Sister	Esophagus		
Case	Female	71	3	1	Sister	Throat[b]	Brother	Throat[b]		
Case	Female	50	0	6	Mother	Throat[b]	Brother	Throat[b]		
Control	Male	79	1	3	Mother	Oral cavity	Brother	Throat[b]		
Control	Male	78	2	5	Father	Throat[b]	Brother	Throat[b]		
Control	Female	54	10	8	Father	Oral cavity	Sister	Throat[b]	Brother	Esophagus
Control	Female	77	0	1	Father	Throat[b]	Mother	Throat[b]		

UADT: upper aerodigestive tract.
[a] Upper aerodigestive tract carcinomas include oral cavity, pharynx, larynx, esophagus, and "throat."
[b] Throat includes pharynx, larynx, and esophagus.

TABLE 3
Risk of Oral and Pharyngeal Cancer According to Family History of Selected Cancers

Family history	Case	Control	OR[a,b]	95% CI
Any first-degree relative				
No family history of any cancer	187	185	1.0	—
Family history				
Any cancer	155	194	1.1	0.7–1.5
Lung carcinoma	9	12	1.1	0.3–3.5
Liver carcinoma	6	12	0.5	0.1–1.9
Stomach carcinoma	25	38	0.9	0.5–1.8
Male reproductive carcinomas	16	23	0.8	0.4–1.9
Female reproductive carcinomas	36	42	1.0	0.6–1.8

OR: odds ratio; CI: confidence interval.
[a] All OR relative to risk of 1.0 for subjects with no family history of any cancer.
[b] All ORs adjusted for age, gender, tobacco, and alcohol.

bles presented in Table 5 were also consistent with a multiplicative model ($P = 0.5$). The risks of oral carcinoma increased with decreasing intake of raw fruits and vegetables among subjects with and without a family history of UADT carcinoma. However, the difference in risk between subjects with and without a family history of UADT carcinoma was greatest among subjects with less frequent intake of raw fruits and vegetables (quartiles 1 and 2). Similar results were obtained when risks were calculated for family history of UADT carcinoma in parents and siblings separately (data not shown). For both smoking/drinking and diet, the combined risks for subjects with a family history of non-UADT carcinoma were similar to the risks for subjects with no family history of cancer (data not shown).

DISCUSSION

In this population-based case–control interview study of oral and pharyngeal carcinoma conducted in Puerto Rico, we found a 2.5-fold excess risk among subjects who reported having a first-degree relative with cancer of the oral cavity and a 2.6-fold excess risk associated with a history of UADT carcinoma in a first-degree relative, but no excess risk associated with a history of UADT carcinoma in a spouse. The increased risks associated with familial occurrence of UADT carcinoma were most pronounced among individuals with established risk factors (i.e., heavy drinking and/or smoking and infrequent intake of raw fruits and vegetables) and among younger (younger than 65 years) rather than older subjects. Significantly elevated risks associated with family history of UADT carcinoma were reported previously in a case–control study of oral, pharyngeal, and laryngeal carcinoma in southern Brazil using hospital controls (OR, 3.6; 95% CI, 2.0–6.8)[11] and in a retrospective cohort study comparing the risk in first-degree relatives of UADT carcinoma cases versus spouses in Canada (relative risk [RR], 3.8; 95% CI, 1.1–13.0).[10] Familial associations also were noted for UADT carcinoma among first-degree relatives of cases versus spouses in The Netherlands (RR, 3.5; 95% CI, 0.8–13.7),[9] for carcinoma of the oral cavity among first-degree relatives from the Utah Population Database (RR, 1.8; 95% CI, 0.5–4.0),[7] and for carcinomas of the oral cavity and larynx

TABLE 4
Joint Odds Ratios for Family History of Upper Aerodigestive Tract Cancer and Categories of Cigarette Smoking and Alcoholic Beverage Use among Puerto Rican Men and Women with Oral or Pharyngeal Carcinoma

		Family history of cancer[a]	
Smoking status[c]	Drinking status[d]	No family history of any cancer, OR[b] (95% CI)	Family history of UADT carcinoma, OR[b] (95% CI)
Light	Light	1.0	1.8 (0.6–5.6)
Light	Heavy	2.1 (0.9–4.6)	11.5 (3.2–40.7)
Heavy	Light	4.3 (2.4–7.8)	12.3 (3.0–51.4)
Heavy	Heavy	12.2 (6.8–21.9)	60.4 (21.0–174.0)

UADT: upper aerodigestive tract; OR: odds ratio; CI: confidence interval.
[a] Excludes subjects with a family history of non-UADT carcinoma.
[b] Adjusted for age and gender.
[c] Light indicates non-cigarette smoker or smoker of < 10 cigarettes per day, or quit 20+ years ago; heavy, cigarette smoker of 10+ cigarettes per day, or quit < 20 years ago, or tobacco users other than cigarettes.
[d] Light, non-alcohol drinker or drank < 8 drinks per week, or quit 20+ years ago; heavy, alcohol drinker of 8+ drinks per day, or quit < 20 years ago.

TABLE 5
Joint Odds Ratios for Family History of Upper Aerodigestive Tract Carcinoma and Frequency of Raw Fruit and Vegetable Consumption among Puerto Rican Men and Women with Oral or Pharyngeal Carcinoma

	Family history of cancer[a]	
Quartiles of raw fruit/vegetable consumption (no. of servings per week)	No family history of cancer, OR[b] (95% CI)	Family history of UADT carcinoma, OR[b] (95% CI)
Quartiles 4—frequent	1.0	0.6 (0.2–2.6)
Quartile 3	1.0 (0.5–2.1)	3.0 (0.8–11.3)
Quartile 2	1.5 (0.7–2.9)	6.7 (1.8–24.1)
Quartile 1—infrequent	2.0 (1.0–3.9)	6.8 (2.0–22.7)

UADT: upper aerodigestive tract; OR: odds ratio; CI: confidence interval.
[a] Excludes subjects with a family history of non-UADT carcinoma.
[b] Adjusted for age, gender, tobacco, and alcohol.

among offspring from the Swedish nationwide family cancer database (RR, 1.7; 95% CI, 0.4–3.0 in offspring of fathers; RR, 2.3; 95% CI, 0.0–5.2 in offspring of mothers).[27] A population-based case–control study of oral and pharyngeal carcinoma in four areas of the United States found nonsignificantly elevated risks associated with a family history of oral and pharyngeal carcinoma (OR, 1.2; 95% CI, 0.7–2.3) and of esophageal and laryngeal carcinoma (OR, 1.6; 95% CI, 0.7–3.8).[8]

We were unable to study family history of specific UADT carcinoma sites except for the oral cavity because of the high number of cancers in family members reported nonspecifically as cancer of the "garganta," translated as throat, a site that could refer to carcinomas located in either the pharynx, larynx, or esophagus. Therefore, our analysis assessed the risks associated with a family history of all UADT carcinomas combined (oral cavity, pharynx, larynx, and esophagus). Using all UADT carcinomas as a category can be justified because these tumors are generally squamous cell in origin and related to excessive drinking and smoking. In addition, a family history of UADT carcinoma has been associated with multifocal occurrences of UADT carcinoma.[28]

Because alcohol and tobacco use aggregates in families,[29–31] it is possible that these factors could account in part for the familial aggregation of UADT carcinomas observed in our study. However, because we did not find familial associations for lung or liver carcinomas, it seems unlikely that the increased risk observed for oral and other UADT carcinomas is fully explained by a familial tendency to smoking or drinking.

Genetic polymorphisms may increase susceptibility to oral and other UADT carcinomas through interactions with alcohol, tobacco, and perhaps dietary components.[17,18,32] Other studies of oral cavity and UADT carcinomas have reported greater mutagen sensitivity (an indicator of genetic instability as measured by the frequency of in vitro bleomycin-induced chromosome breaks in lymphocytes) among patients with a family history of cancer.[12,13,33] Because mutagen sensitivity appears to be an inherited trait,[34] these observations suggest the role of genetic instability as a risk factor for oral and other UADT carcinomas. The risk associated with mutagen sensitivity appears to be independent of age, gender, alcohol, tobacco, and diet.[34,35] An interactive effect on oral carcinoma risk from dietary nutrients (particularly vitamins C and E) and mutagen sensitivity was shown in a case–control study by Schantz et al.[34] In our study, we observed a reduced risk (OR, 0.6) of oral carcinoma among sub-

jects with a family history of UADT carcinoma who were also frequent consumers of raw fruits and vegetables.

In addition, a segregation analysis conducted among first-degree relatives of UADT carcinoma cases and spouse controls in Canada was more consistent with a "major gene" model than a purely environmental effect.[16] According to this model, it was estimated that subjects who drink and smoke and carry a highly penetrant cancer gene have a 78% risk of developing UADT carcinoma by age 70 compared with a 5% risk for subjects who drink and smoke but do not carry the high-risk genotype. Linkage analysis in UADT carcinoma families may provide opportunities to identify the responsible genes.

The strengths of our study include the use of a population-based series of cases with newly diagnosed carcinomas of the oral cavity and pharynx, in-person interviews conducted directly with all cases and controls, and quantitative estimates based on cancers reported in first-degree relatives only. The limitations of our study include the lack of validation for in-person interviews used for collecting family cancer history, the likely underreporting of cancer in these relatives, and the potential for heightened recall of cases versus controls. However, several studies have shown that subjects in case–control studies are able to report family histories among first-degree relatives with common types of cancer with little observable recall bias.[36–38] Also, reports of UADT carcinoma among relatives may be fairly accurate because these tumors often are associated with functional impairment, disfigurement, prolonged rehabilitation, and death.[10]

In our study, the percentage of controls reporting any form of cancer in a parent or sibling was slightly less (37%) than that reported in a U.S. population-based study of oral and pharyngeal carcinoma (41%),[8] and in a U.S. study of UADT carcinomas using blood donor controls (49%),[13] even though the average family size was larger in our study. Furthermore, based on Puerto Rico incidence data, there appears to be underreporting of lung and prostate carcinomas in our study population since the rates of these tumors should exceed the rates for stomach carcinoma.[1] Although we lacked information on the smoking and drinking habits of relatives, if there is a familial propensity to drink or smoke, then controlling for the subject's alcohol and tobacco habits would partially control for the habits of their relatives.[11] In addition, a cohort study of UADT carcinoma in Canada found that relatives of cases were only slightly more likely to be smokers (53% vs. 50%) or drinkers (29% vs. 26%) than relatives of spouses.[10] In that study, addition of smoking and drinking data on relatives to the model containing the subject's smoking and drinking data did not alter the magnitude of the increased risk for developing UADT carcinoma among family members.

In summary, our case–control study in Puerto Rico revealed a familial tendency to oral cavity and other UADT carcinomas, although it was difficult to distinguish between the effects of inherited susceptibility, shared lifestyle exposures, or a combination of these factors. This finding provides support for studies aimed at gene identification through linkage disequilibrium approaches in high-risk families, and gene–environment interactions through association studies in populations. Although a heritable component to oral and other UADT carcinomas seems likely, it is important that at-risk family members understand that their vulnerability to these tumors can be greatly reduced by tobacco cessation, moderation of alcohol drinking, and frequent intake of raw fruits and vegetables based on current knowledge of risk factors and gene–environment interactions.

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